Remarks

Support for the Amendments

Support for the foregoing amendments to claims 1, 3, 4, 6, 8 and 17 can be found throughout the specification. Support for new claims 18-48 can be found throughout the specification. These amendments do not add new matter, and their entry and consideration are respectfully requested.

Status of the Claims

By the foregoing amendments, claims 1, 3, 4, 6, 8 and 17 are sought to be amended, and new claims 18-48 are sought to be added. Upon entry of the foregoing amendments, claims 1, 3-9, 15-17 and 18-48 are pending in the application, with claims 1, 3, 4, 18, 23 and 28 being the independent claims.

Summary of the Office Action

In the Office Action dated June 3, 2004, the Examiner has made three rejections of the claims. Applicants respectfully offer the following remarks to traverse each of these elements of the Office Action.

The Rejection Under 35 U.S.C. § 102(b) Over Zubiaga

In the Office Action at pages 2-3, the Examiner has rejected claims 4, 6, 16 and 17 under 35 U.S.C. § 102(b), as allegedly being anticipated by Zubiaga *et al.* (*Mol. Cell. Biol. 15*:2219-2230 (1995); hereinafter "Zubiaga"). Applicants respectfully traverse this rejection.

The Examiner contends that Zubiaga discloses an expression vector comprising a *c-fos* promoter operatively linked to a globin gene, wherein an ARE sequence is inserted into the 3′ UTR of the globin gene. The Examiner further contends that Zubiaga discloses a control plasmid comprising a gene encoding for expression of *lacZ*, but lacking an mRNA instability sequence, and that these constructs are transfected into NIH-3T3 cells. The Examiner therefore concludes that Zubiaga discloses the present invention. Applicants respectfully disagree with these contentions and conclusions.

Present claim 4 (and hence, claims 6, 16 and 17 that depend ultimately therefrom and that are also rejected) recites a reporter gene DNA expression system which comprises an expression cassette consisting of one or more reporter genes encoding a protein which gives a detectable signal. Claim 4 further recites that an instability region is inserted into the 3′ UTR sequence of the reporter gene.

Applicants respectfully submit that Zubiaga does not disclose an expression cassette consisting of one or more reporter genes encoding a protein which gives a detectable signal. The disclosure of Zubiaga is directed toward the use of a plasmid construct that encodes the β-globin protein. Zubiaga does not disclose an expression cassette comprising a reporter gene which encodes a protein which gives a detectable signal.

Furthermore, the plasmid construct disclosed in Zubiaga does not consist of an instability region inserted into the 3′ UTR sequence of a reporter gene, as recited in the present claims. Instead, the construct of Zubiaga consists of a 53 base-pair spacer region between the β-globin coding region and an ARE sequence inserted prior to the 3′ UTR of the gene. (*see* Zubiaga at page 2220, right hand column, last four lines). Hence, the ARE

sequence is not inserted *into* the 3′ UTR sequence of the reporter gene as required in the present claims, but instead is fused *between* the β-globin gene and its corresponding 3′ UTR sequence.

Hence, Zubiaga does not disclose all of the elements of the presently claimed invention. Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Since Zubiaga does not expressly or inherently disclose one or more elements of the presently claimed invention, this reference cannot, and does not, anticipate the present claims. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Zubiaga are respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Banholzer, Zubiaga and Zhang

In the Office Action at pages 4-5, the Examiner has rejected claims 1, 3 and 15 under 35 U.S.C. § 103(a), as being unpatentable over Banholzer (*Molec. Cell. Biol. 17*:3254-3260 (1997); hereinafter "Banholzer") in view of Zubiaga, and further in view of Zhang *et al.* (*Biochem. Biophys. Res. Comm. 227*:707-711 (1996); hereinafter "Zhang"). Applicants respectfully traverse this rejection.

The Examiner notes that the screening method of Banholzer does not disclose an expression system comprising a reporter gene, wherein the detectable signal of the encoded protein is measured for determining whether the compounds affect mRNA stability. The Examiner further states that Banholzer does not disclose an mRNA instability sequence that

is heterologous to the 3′ UTR of the reporter gene. (*See* Office Action at page 4, fourth paragraph.) The Examiner therefore relies on the disclosures of Zubiaga and Zhang to cure these deficiencies. The Examiner contends that it would have been obvious to utilize the green fluorescent protein (GFP) reporter gene disclosed in Zhang in the screening method of Banholzer. The Examiner further contends that since the ARE instability region disclosed in Zubiaga can be inserted into the 3′ UTR of any gene, it would have been *prima facie* obvious to insert such a sequence into a GFP gene and utilize this construct in the methods of Banholzer. The Examiner asserts that the ordinarily skilled artisan would have been motivated to make these modifications because of the advantages offered by a GFP reporter gene versus measuring mRNA stability by Northern blot analysis. The Examiner therefore concludes that these references in combination render the present invention obvious to one of ordinary skill in the art. Applicants respectfully disagree with these assertions and conclusions.

The Examiner correctly states that Banholzer does not disclose methods wherein the detectable signal of an encoded protein is measured. Applicants respectfully submit that the ordinarily skilled artisan would not have been motivated to utilize the GFP reporter gene disclosed in Zhang in the practice of the methods disclosed in Banholzer. Banholzer provides no indication that such a modification would be desirable or necessary. The methods disclosed in Banholzer require the use of Northern blot analysis to determine mRNA levels. The ordinarily skilled artisan would not have been motivated to utilize a GFP reporter protein, and the detectable signal generated by it, in the methods of Banholzer, as the analysis disclosed in Banholzer requires the quantification of mRNA via Northern

blotting. Furthermore, as noted above, Zubiaga does not disclose the use of a reporter gene that expresses a protein which gives a detectable signal. Thus, the deficiencies in Banholzer cannot be cured by the disclosure of Zhang, or Zubiaga, alone or in combination, and hence the Examiner has not established a *prima facie* case of obviousness.

In addition, as the Examiner has noted, Banholzer does not disclose the insertion of an mRNA instability sequence that is heterologous to the 3′ UTR of the reporter gene. The Examiner relies on the disclosure of Zubiaga to cure this deficiency. Applicants respectfully submit that there is no motivation in the disclosure of Banholzer to insert the mRNA instability sequences disclosed in Zubiaga into the plasmids used in the methods of Banholzer. The methods of Banholzer do not suggest the insertion of heterologous instability regions into the 3′ UTR sequence of a reporter gene, focusing instead on the use of a gene that naturally comprises an instability region. Furthermore, as noted above, Zubiaga does not actually disclose the insertion of instability regions into the 3′ UTR sequence of a reporter gene, and hence could not be combined with Banholzer to render obvious the presently claimed invention. As there is no motivation to combine to the disclosure of Banholzer with that of Zubiaga, the Examiner has not established a *prima facie* case of obviousness. Furthermore, the combination of Banholzer and Zubiaga do not teach all of the limitations of the present claims, and hence cannot render obvious the present claims.

These serious deficiencies in Banholzer discussed above are not cured by the disclosure of Zhang. Zhang does not disclose, suggest or contemplate the insertion of a heterologous instability region into the 3′ UTR sequence of a reporter gene. Hence,

Applicants respectfully submit that the ordinarily skilled artisan would not have obtained the presently claimed invention by combining these two references.

In view of the foregoing remarks, Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness, and hence claims 1, 3 and 15 would not have been obvious over the disclosures of Banholzer, Zubiaga and Zhang, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) therefore are respectfully requested.

The Rejection Under 35 U.S.C. § 103(a) Over Zubiaga in view of Maniatis

In the Office Action at pages 5-6, the Examiner has rejected claims 5 and 7-9 under 35 U.S.C. § 103(a) as being unpatentable over Zubiaga in view of Maniatis *et al.* (Molecular Cloning, A Laboratory Manual, p 16.33-16.17 (1989); hereinafter "Maniatis"). Applicants respectfully traverse this rejection.

The Examiner contends that it would have been obvious to stably transfect a cell line with the plasmid constructs disclosed in Zubiaga based upon the disclosure of Maniatis. The Examiner therefore concludes that the presently claimed invention would have been obvious in view of these two references. Applicants respectfully disagree with this conclusion.

As noted above, Zubiaga does not disclose an expression cassette comprising a reporter gene which encodes a protein which gives a detectable signal. Furthermore, the plasmid construct disclosed in Zubiaga does not consist of an instability region inserted into the 3′ UTR sequence of the reporter gene as recited in the present claims. For at least these reasons, Zubiaga is seriously deficient as a primary reference on which to base a *prima face*

case of obviousness. These serious deficiencies in Zubiaga are not cured by the disclosure of Maniatis, as Maniatis only discloses a method of stably transfecting cells.

Hence, the disclosures of Zubiaga and Maniatis, alone or in combination, cannot render obvious the presently claimed invention. In view of the arguments presented above, Applicants submit that the Examiner has not established a *prima facie* case of obviousness, and therefore reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

In the event the Examiner determines that the present application is not in condition for immediate allowance, Applicants respectfully request that Examiner contact the undersigned at the number provided in order to schedule an interview.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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